Epidemiology of Contrast-Induced Nephropathy

Peter A. McCullough, MD, MPH, FACC, FACP, FCCP, FAHA,
Keisha R. Sandberg, MPH

Department of Medicine, Divisions of Cardiology, Nutrition, and Preventive Medicine, William Beaumont Hospital, Royal Oak, MI

Decreasing levels of renal function act as a major adverse prognostic factor after contrast exposure with or without percutaneous coronary intervention. In chronic kidney disease, the most important risk factor for the development of contrast-induced nephropathy (CIN) is an estimated glomerular filtration rate ≤ 60 mL/min/1.73 m^2. Additional risk factors include diabetes, proteinuria, volume depletion, heart failure, and intraprocedural events. Overall, CIN occurs in approximately 15% of radiocontrast procedures, with < 1% requiring dialysis. CIN is directly related to increases in hospitalization length, cost, and long-term morbidity. For those patients who require dialysis, a 30% in-hospital mortality rate and 80% 2-year mortality rate can be expected. CIN is predictable and presents an opportunity to utilize preventive strategies, given the increasing numbers of patients undergoing contrast procedures worldwide.
[Rev Cardiovasc Med. *2003;4(suppl 5):S3–S9*]

Key words: Cardiovascular disease • Chronic kidney disease • Acute renal failure • Contrast-induced nephropathy • Microalbuminuria • Dialysis

The modern pandemics of obesity and hypertension in industrialized nations are the central drivers of a secondary epidemic of combined chronic kidney disease (CKD) and cardiovascular disease (CVD).[1] Approximately one half of all cases of end-stage renal disease (ESRD) are due to diabetic nephropathy, with most of these cases driven by obesity-related type 2 diabetes and hypertension.[1] With cardiovascular care shifting towards the

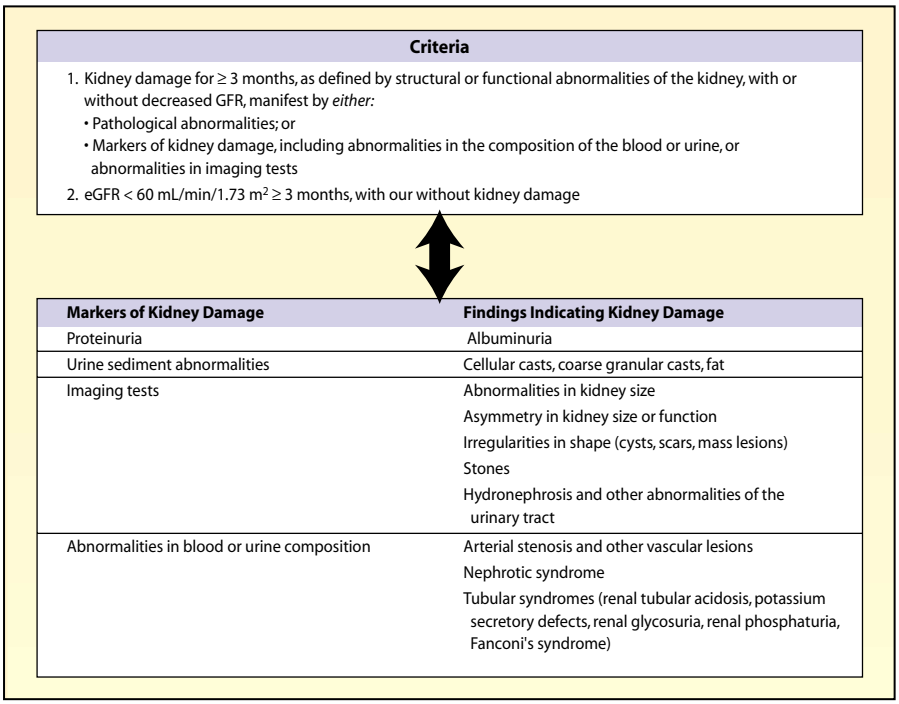


Figure 1. *The criteria for chronic kidney disease (CKD) according to the National Kidney Foundation Kidney Disease Outcomes Quality Initiative (KDOQI). Increased rates of adverse events are generally seen below an estimated glomerular filtration rate (eGFR) of 60 mL/min/1.73 m². GFR, glomerular filtration rate. Reprinted with permission from the National Kidney Foundation.*[3]

growing elderly population, it is imperative to understand why decreasing levels of renal function act as a major adverse prognostic factor after contrast exposure with or without peripheral or percutaneous coronary intervention (PCI).[2] As the most proximal renal event, acute renal failure is predictable and provides an opportunity to utilize preventive strategies outlined in this supplement.

Chronic Kidney Disease: Defining a Critical Level of Risk

CKD is defined as an estimated glomerular filtration rate (eGFR) ≤ 60 mL/min/1.73 m², or by the presence of microalbuminuria/proteinuria (random spot urine albumin to creatinine ratio of > 30 mg/g) (Figure 1).[3] Most studies of cardiovascular outcomes confirmed a breakpoint in eGFR of 60 mL/min/1.73 m² for the development of contrast-induced nephropathy (CIN), later restenosis, recurrent myocardial infarction, diastolic/systolic congestive heart failure (CHF), and cardiovascular death.[4–7] This roughly corresponds to a serum creatinine (SCr) level of > 1.5 mg/dL in the general population.

However, serum creatinine can be amazingly deceptive in the elderly. As Table 1 depicts, the threshold of an eGFR of 60 mL/min/1.73 m² can be found at a SCr < 1.0 mg/dL in those over age 80. Calculated measures of eGFR or creatinine clearance (CrCl) are critical to understanding the epidemiology and risks of CIN. The Modification of Diet in Renal Disease (MDRD) equation, the preferred method for these calculations as it does not rely on measured body weight and is available on commercial laboratory reports and on personal digital assistants (PDAs), is given below[3]:

$$(186.3 * [\text{serum creatinine}^{-1.154}] * [\text{age}^{-.203}])$$

Calculated value is multiplied by .742 for women and by 1.21 for African Americans.

In addition, microalbuminuria at any level of eGFR represents CKD and most likely occurs as a result of hyperfiltration in the kidneys due to diabetes and hypertension-related changes in the glomeruli.[8] It is critical to understand that CIN risk is related in a curvilinear fashion to the

Table 1
Serum Creatinine Corresponding to an eGFR of 60 mL/min/1.73 m²

	European American		African American	
Age (y)	Men	Women	Men	Women
30	1.47	1.13	1.73	1.34
40	1.39	1.08	1.65	1.27
50	1.34	1.03	1.58	1.22
60	1.30	1.00	1.53	1.18
70	1.26	0.97	1.49	1.15
80	1.23	0.95	1.46	1.12

Calculations in this table assume a weight of 72 kg and body surface area of 1.73 m². Units for serum creatinine are mg/dL (multiply by 88.4 μmol/L = 1 mg/dL).
Reprinted with permission from the National Kidney Foundation.[3]

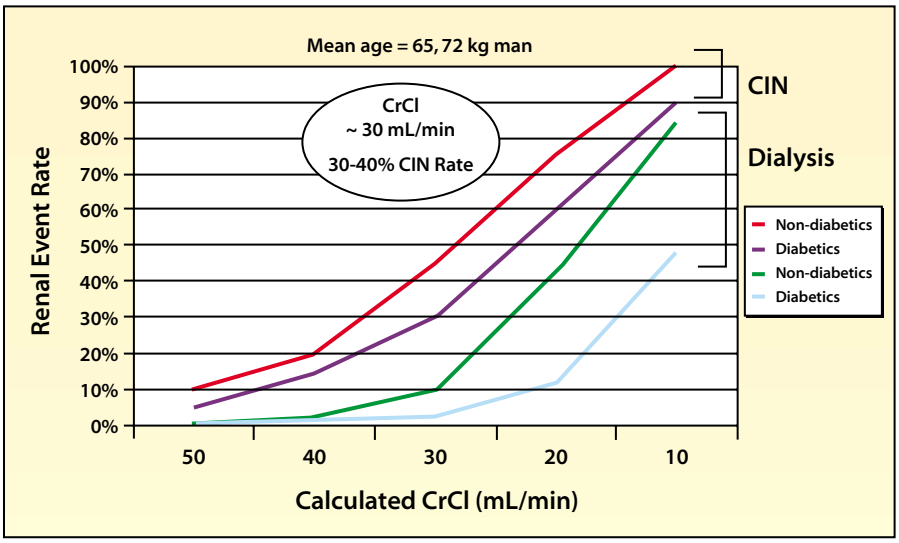


Figure 2. *Validated risk of acute renal failure requiring dialysis after diagnostic angiography and ad-hoc angioplasty. A mean contrast dose of 250 mL and a mean age of 65 is assumed. CrCl, creatinine clearance; CIN, contrast-induced nephropathy. Data adapted from McCullough et al[9] and Rihal et al.[10]*

eGFR as shown in Figure 2.[9–10] Among all patients taken to the cardiac catheterization laboratory, approximately 15% will develop CIN (Table 2).[9,11–15] Furthermore, CIN risk is approximately the same for renal and peripheral vascular procedures, as indicated in Table 2. With over 1,000,000 procedures performed annually in the United States, the incidence of CIN is over 150,000 cases per year.

Risk Factors for Contrast Nephropathy

The level of renal dysfunction, best expressed in terms of eGFR as outlined above, is the most important risk factor for the development of CIN.[9] An eGFR of 60 mL/min/1.73 m^2 corresponds to a serum creatinine of 1.30 and 1.00 in a 60-year-old male and female, respectively (Table 1). After eGFR has been considered, other risk factors influence outcomes, but to a lesser extent. These risk factors include diabetes, duration of diabetes, urine albumin/creatinine ratio (ACR), hypertension, a history of structural kidney disease or damage, congestive heart failure, and preprocedural volume depletion. Also, several procedural factors add injury and behave as risk factors in the causal pathway of acute renal failure. These factors include intraprocedural hypotension, use of intra-aortic counterpulsation, cholesterol emboli syndrome, and use of large volumes of contrast (Table 3). Probably the most underappreciated event is atherosclerotic emboli dislodged when a catheter is passed through the aorta, which occurs in approximately 50% of cases, most of which are clinically silent.[16] Although proposed, a limit of contrast beyond which CIN can occur has never been confirmed. In fact, as the eGFR declines, lesser amounts of contrast are needed to induce CIN. When the eGFR drops to < 30 mL/min/1.73 m^2, approximately 15 cc to 30 cc of contrast can trigger CIN leading to dialysis.[17] Importantly, in the absence of contrast, hypotension and prolonged durations of cardiopulmonary bypass are related to acute renal failure after coronary artery bypass graft surgery in patients at risk (eGFR < 60 mL/min/1.73 m^2).[6,18]

Contrast-Induced Nephropathy or "Benign Creatininopathy"?

The most common definitions of CIN are a rise in SCr > 25% from baseline, or by an absolute increase from baseline of > 0.5 mg/dL. In 80% of cases, this rise occurs within the first 24 hours.[19] Nearly all patients who progress to serious renal failure requiring either nephrology consultation or dialysis have a rise in SCr within the first 24 hours.[19] The trajectory of this rise commonly peaks

Table 2
Rates of Contrast-Induced Nephropathy (CIN) in Renal Vascular and Peripheral Procedures

Author	Year	No. of Patients	Vascular Bed	CIN Definition	CIN Rate
McCullough et al[9]	1997	3695	Coronary	> 25% rise	14.8%
Cochran et al[11]	1983	266	Renal	> 20% rise or > 0.3 mg/dL	16.9%
Schillinger et al[12]	2001	213	Peripheral	≥ 20% decrease CrCl	12.0%
Sabeti et al[13]	2002	85	Renal	≥ 33% rise in 24 h	15.0%
Lufft et al[14]	2002	47	Renal	> 25% rise	12.8%
Lufft et al[15]	2002	80	Renal	> 25% rise or > 0.5 mg/dL	7.8%

The most common definitions of CIN are a rise in SCr > 25% from baseline or by an absolute increase from baseline of > 0.5 mg/dL prior to contrast exposure. CR, creatinine; CrCl, creatinine clearance.

Table 3
Risk Factors for the Development of Contrast-Induced Nephropathy

- eGFR ≤ 60 mL/min/1.73 m²
- Diabetes
- Urine ACR > 30
- Hypertension
- History of structural kidney disease or damage
- Congestive heart failure
- Preprocedural volume depletion
- Intraprocedural hypotension
- Intra-aortic counterpulsation
- Cholesterol emboli syndrome
- Use of large volume of contrast

ACR, urine albumin-creatinine ratio; eGFR, estimated glomerular filtration rate.

at 48 hours to 96 hours after contrast exposure (Figure 3). We and others have demonstrated that the overall risk of CIN, defined as a transient rise in SCr > 25% above the baseline, occurs in approximately 13% of nondiabetics and 20% of diabetics undergoing PCI (Figure 2).[9] Fortunately, the overall rates of CIN leading to dialysis are low (0.5%–2.0%). Yet, when they occur, they are related to catastrophic outcomes, including a 36% in-hospital mortality rate and a 2-year survival rate of only 19%.[9] Approximately one half of dialysis cases are transient, and one half result in permanent dialysis dependency. However, the high mortality rate is unchanged whether the dialysis is permanent or temporary.[9] The mortality rate for acute renal failure requiring dialysis after contrast exposure is consistent with the high rates observed in other series of acute in-hospital renal failure (Table 4).[9,20–26] Therefore, a "benign creatininopathy" or asymptomatic rise in SCr can be the beginning of fatal complications.[27]

Small Rises in Creatinine Are Linked to Poor Long-Term Outcomes

Transient rises in SCr are directly related to longer intensive care unit and hospital ward stays (3 and 4 more days, respectively) after bypass surgery.[18] Even transient rises in SCr translate to differences in adjusted long-term outcomes after PCI (Figure 4).[10] What is happening in this population? The leading theory suggests that as renal function declines, the associated abnormal vascular pathobiology accelerates. Hence, progression of CVD events occurs at a higher rate. End-organ protection as a strategy not only to reduce in-hospital complications, but to influence long-term outcomes, is an intriguing issue.[28]

Chronic Care Impacts Renal Outcomes

Long-term cardiorenal protection involves two important concepts; blood pressure control in CKD to a target of ~125/75 mm Hg,[29] and use of an agent that blocks the renin-angiotensin system (RAS), such as an angiotensin-converting enzyme inhibitor (ACEI) or an angiotensin receptor blocker (ARB) as the base of therapy.[30] Importantly, in approximately 10% of cardiovascular patients, both agents cause a chronic rise in SCr > 25% above the baseline.[31] Despite the rise in SCr, there are large

Nearly all patients who progress to serious renal failure requiring either nephrology consultation or dialysis have a rise in SCr within the first 24 hours.

Figure 3. *Trajectory of serum creatinine (SCr) after contrast exposure in 3 sample patients with differing levels of renal function: Patient A: eGFR > 60 mL/min/1.73 m²; Patient B: eGFR 30–60 mL/min/1.73 m²; Patient C: eGFR < 30 mL/min/1.73 m². Note that each patient started with a serum SCr of 1.0 mg/dL at baseline and definitions of contrast-induced nephropathy were met by patients B and C at 24 hours.*
eGFR, estimated glomerular filtration rate; LOS, length of hospital stay.

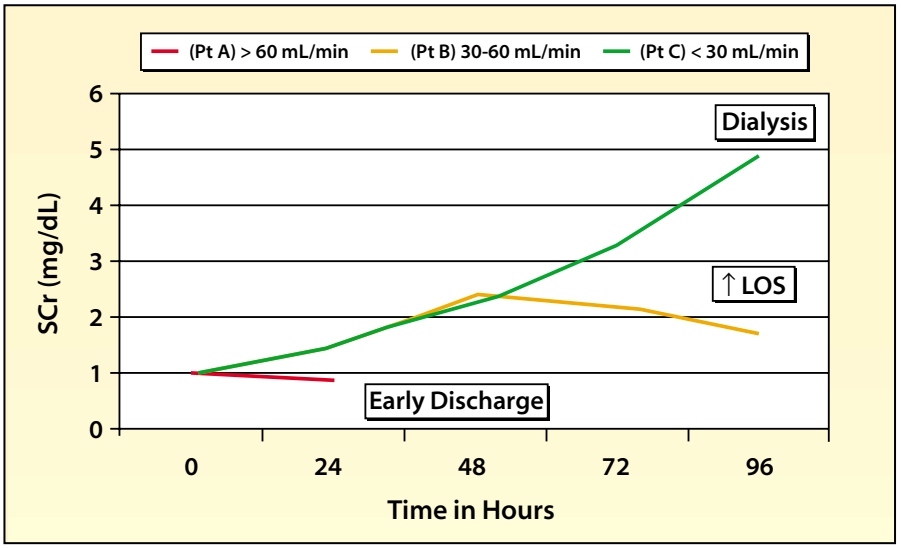


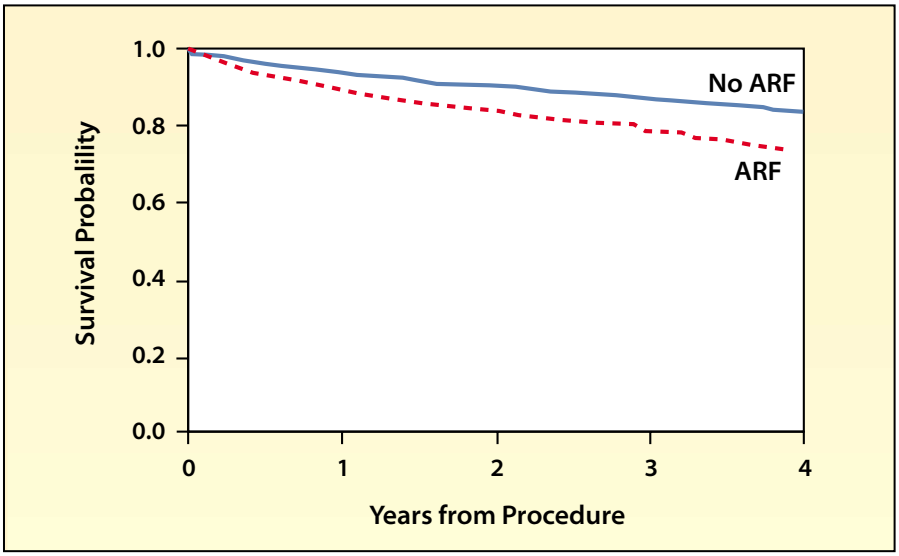
Table 4
Rates of Contrast-Induced Nephropathy in Renal Vascular and Peripheral Procedures

Author	Year	No. of Patients	Setting	Dialysis Rate	Mortality
McCullough et al[9]	1997	3695	Catheterization laboratory	0.5%	37.0%
Gruberg et al[20]	2000	12,054	Catheterization laboratory	0.4%	25.5%
Levy et al[21]	1996	16,248	Radiologic contrast studies	1.1%	34.0%
Douma et al[22]	1997	238	ICU	—	76.0%
Rialp et al[23]	1996	1087	ICU	5.9%	71.5%
Andersson et al[24]	1993	2009	CABG	1.2%	44.0%
Chertow et al[25]	1997	43,642	CABG	1.1%	63.7%
Joachimsson et al[26]	1989	5181	CABG	1.4%	57.0%

CABG, coronary artery bypass surgery; ICU, intensive care unit.

benefits to ACEI/ARB agents in reducing new cases of end-stage renal disease (ESRD), congestive heart failure, or cardiovascular death.[32–35] These benefits extend to nondiabetics and to African Americans with CKD.[36–38] Toxin removal largely refers to discontinuation of nonsteroidal anti-inflammatory agents, aminoglycosides, and cyclosporin. These agents complicate cardiovascular procedures and increase the risk of CIN. Prevention measures taken prior to PCI include hydration, measures to reduce the direct cellular toxicity of the contrast, and, importantly, measures to reduce the intrarenal vasoconstriction occurring uniquely in CKD patients when exposed to iodinated contrast.[9] Based on the totality of evidence to date, if a patient can be carried through a cardiovascular procedure (PCI or bypass surgery) without a rise in SCr, shorter hospitalization and improved long-term survival can be expected.[6,9,10,16–18]

Figure 4. *Adjusted, long-term outcomes in 7586 patients with and without acute renal failure after angioplasty, P < .0001. Acute renal failure is defined as a ≥ 0.5 mg/dL rise in creatinine after percutaneous coronary intervention. ARF, acute renal failure; MI, myocardial infarction. Reprinted with permission from Rihal et al.[10]*



Prevention of Contrast-Induced Nephropathy

For patients with significant CKD—baseline eGFR < 60 mL/min/1.73 m^2 or urine ACR > 30 mg/g—use of a CIN prevention strategy is advised. In general, at an eGFR of 30 mL/min/1.73 m^2, the expected rate of CIN is 30% to 40% and the rate of acute renal failure requiring dialysis is 2% to 8%. Quality improvement efforts in this area favorably impact outcomes and the bottom line of any program (Figure 5).[20] There are four basic concepts in CIN prevention: (1) hydration, (2) choice and quantity of contrast, (3) pre-, intra-, and postprocedural end-organ protection with pharmacotherapy, and (4) postprocedural monitoring and expectant care. These issues will be explored in detail in subsequent articles in this supplement.

Conclusion

Chronic kidney disease is the most important factor in predicting adverse short- and long-term out-

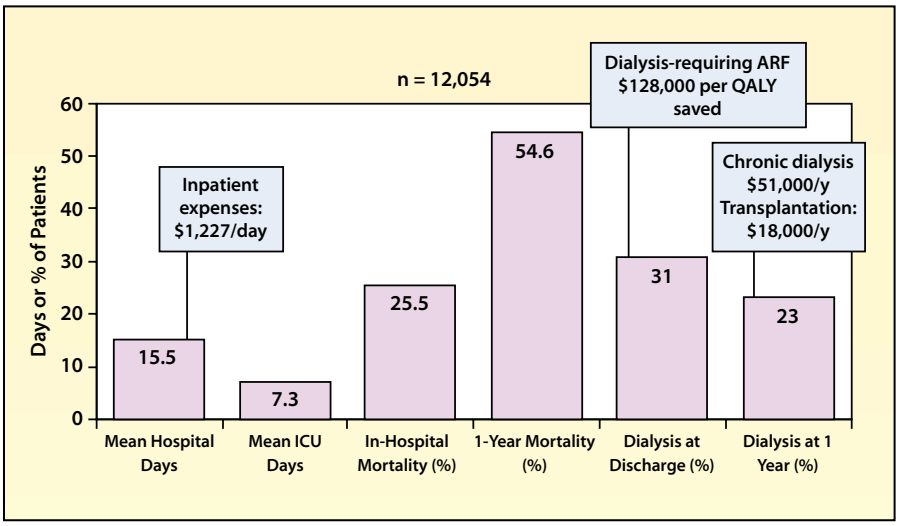


Figure 5. *Impact of contrast-induced nephropathy that results in dialysis on clinical and economic outcomes. Reprinted with permission from Gruberg et al.*[20]
ARF, acute renal failure; ICU, intensive care unit; QALY, quality adjusted life years.

comes after PCI. The most important risk factor for the development of CIN is reduced renal function. Additive risk factors include diabetes vintage, proteinuria, volume depletion, heart failure, and intraprocedural events including hypotension, use of intra-aortic balloon counterpulsation, cholesterol emboli, and high volumes of contrast. The rationale for renal end-organ protection is based on chronic renal protection, avoidance of additive renal insults, and a comprehensive approach to CIN prophylaxis. ■

References

1. Bakris GL, Williams M, Dworkin L, et al. Preserving renal function in adults with hypertension and diabetes: a consensus approach. National Kidney Foundation Hypertension and Diabetes Executive Committees Working Group. *Am J Kidney Dis*. 2000;36:646–661.
2. McCullough PA. Why is chronic kidney disease the "spoiler" for cardiovascular outcomes? *J Am Coll Cardiol*. 2003;41:725–728.
3. National Kidney Foundation. Clinical practice guidelines for chronic kidney disease: evaluation, classification, and stratification. *Am J Kid Disease*. 2002;2(suppl 1):S46–S75.
4. McCullough PA, Soman SS, Shah SS, et al. Risks associated with renal dysfunction in patients in the coronary care unit. *J Am Coll Cardiol*. 2000;36:679–684.
5. Beattie JN, Soman SS, Sandberg KR, et al. Determinants of mortality after myocardial infarction in patients with advanced renal dysfunction. *Am J Kidney Dis*. 2001;37:1191–1200.
6. Chertow GM, Lazarus JM, Christiansen CL, et al. Preoperative renal risk stratification. *Circulation*. 1997;95:878–884.
7. Szczech LA, Best PJ, Crowley E, et al for the Bypass Angioplasty Revascularization Investigation (BARI) Investigators. Outcomes of patients with chronic renal insufficiency in the bypass angioplasty revascularization investigation. *Circulation*. 2002;105:2253–2258.
8. Keane WF, Eknoyan G. Proteinuria, albuminuria, risk, assessment, detection, elimination (PARADE): a position paper of the National Kidney Foundation. *Am J Kidney Dis*. 1999; 33:1004–1010.
9. McCullough PA, Wolyn R, Rocher LL, et al. Acute renal failure after coronary intervention: incidence, risk factors, and relationship to mortality. *Am J Med*. 1997;103:368–375.
10. Rihal CS, Textor SC, Grill DE, et al. Incidence and prognostic importance of acute renal failure after percutaneous coronary intervention. *Circulation*. 2002;105:2259–2264.
11. Cochran ST, Wong WS, Roe DJ. Predicting angiography-induced acute renal function impairment: clinical risk model. *Am J Roentgenol*. 1983;141:1027–1033.
12. Schillinger M, Haumer M, Mlekusch W, et al. Predicting renal failure after balloon angioplasty in high-risk patients. *J Endovasc Ther*. 2001;8:609–614.
13. Sabeti S, Schillinger M, Mlekusch W, et al. Reduction in renal function after renal arteriography and after renal artery angioplasty. *Eur J Vasc Endovasc Surg*. 2002;24:156–160.
14. Lufft V, Hoogestraat-Lufft L, Fels LM, et al. Angiography for renal artery stenosis: no additional impairment of renal function by angioplasty. *Eur Radiol*. 2002;12:804–809.
15. Lufft V, Hoogestraat-Lufft L, Fels LM, et al. Contrast media nephropathy: intravenous CT angiography versus intraarterial digital subtraction angiography in renal artery stenosis: a prospective randomized trial. *Am J Kidney Dis*. 2002;40:236–242.
16. Keeley EC, Grines CL. Scraping of aortic debris by coronary guiding catheters: a prospective evaluation of 1,000 cases. *J Am Coll Cardiol*. 1998;32:1861–1865.
17. Manske CL, Sprafka JM, Strony JT, Wang Y. Contrast nephropathy in azotemic diabetic patients undergoing coronary angiography. *Am J Med*. 1990;89:615–620.
18. Mangano CM, Diamondstone LS, Ramsay JG, et al. Renal dysfunction after myocardial revascularization: risk factors, adverse outcomes, and hospital resource utilization. The Multicenter Study of Perioperative Ischemia Research Group. *Ann Intern Med*. 1998; 128:194–203.
19. Guitterez N, Diaz A, Timmis GC, et al. Determinants of serum creatinine trajectory in acute contrast nephropathy. *J Interv Cardiol*. 2002;15:349–354.
20. Gruberg L, Mehran R, Dangas G, et al. Acute renal failure requiring hemodialysis after percutaneous coronary intervention: in-hospital and one-year outcomes. *J Am Coll Cardiol*. 2000;35(2 suppl A):53.
21. Levy EM, Viscoli CM, Horwitz RI. The effect of

Main Points

- Renal dysfunction is accurately recognized by calculating the estimated glomerular filtration rate (eGFR) from age, serum creatinine, gender, race, and weight—not from serum creatinine alone.
- Overall, contrast-induced nehpropathy (CIN) occurs in ~15% of radiocontrast procedures with < 1% requiring dialysis.
- The major risk factor for CIN is an eGFR rate < 60 mL/min/1.73 m^2.
- Additive risk factors include diabetes vintage, proteinuria, volume depletion, heart failure, and intraprocedural events including hypotension, use of intra-aortic balloon counterpulsation, cholesterol emboli, and high volumes of contrast.

acute renal failure on mortality. A cohort analysis. *JAMA*. 1996;275:1489–1494.
22. Douma CE, Redekop WK, van der Meulen JH, et al. Predicting mortality in intensive care patients with acute renal failure treated with dialysis. *J Am Soc Nephrol*. 1997;8:111–117.
23. Rialp G, Roglan A, Betbese AJ, et al. Prognostic indexes and mortality in critically ill patients with acute renal failure treated with different dialytic techniques. *Ren Fail*. 1996;18:667–675.
24. Andersson LG, Ekroth R, Bratteby LE, et al. Acute renal failure after coronary surgery—a study of incidence and risk factors in 2009 consecutive patients. *Thorac Cardiovasc Surg*. 1993;41:237–241.
25. Chertow GM, Lazarus JM, Christiansen CL, et al. Preoperative renal risk stratification. *Circulation*. 1997;95:878–884.
26. Joachimsson PO, Stahle E, Nystrom SO, Tyden H. Incidence of acute renal failure in open heart surgery. *J Cardiothorac Anesth*. 1989;3(5 suppl 1):58.
27. Conti CR. Contrast nephropathy or contrast creatininopathy. *Clin Cardiol*. 2003;26:53–54.
28. McCullough PA. Cardiorenal risk: an important clinical intersection. *Rev Cardiovasc Med*. 2002;3:71–76.
29. The sixth report of the Joint National Committee on prevention, detection, evaluation, and treatment of high blood pressure. *Arch Intern Med*. 1997;157:2413–2446.
30. Garg J, Bakris GL. Angiotensin converting enzyme inhibitors or angiotensin receptor blockers in nephropathy from type 2 diabetes. *Curr Hypertens Rep*. 2002;4:185–190.
31. Pitt B, Segal R, Martinez FA, et al. Randomised trial of losartan versus captopril in patients over 65 with heart failure (Evaluation of Losartan in the Elderly Study, ELITE). *Lancet* 1997;349:747–752.
32. Toto R. Angiotensin II subtype 1 receptor blockers and renal function. *Arch Intern Med*. 2001;161:1492–1499.
33. Mann JF, Gerstein HC, Pogue J, et al. Renal insufficiency as a predictor of cardiovascular outcomes and the impact of ramipril: the HOPE randomized trial. *Ann Intern Med*. 2001;134:629–636.
34. Brenner BM, Cooper ME, de Zeeuw D, et al, for the RENAAL Study Investigators. Effects of losartan on renal and cardiovascular outcomes in patients with type 2 diabetes and nephropathy. *N Engl J Med*. 2001;345:861–869.
35. Lewis EJ, Hunsicker LG, Clarke WR, for the Collaborative Study Group. Renoprotective effect of the angiotensin-receptor antagonist irbesartan in patients with nephropathy due to type 2 diabetes. *N Engl J Med*. 2001;345:851–860.
36. Parving HH, Lehnert H, Brochner-Mortensen J, et al, for the Irbesartan in Patients with Type 2 Diabetes and Microalbuminuria Study Group. The effect of irbesartan on the development of diabetic nephropathy in patients with type 2 diabetes. *N Engl J Med*. 2001;345:870–878.
37. Dahlof B, Devereux RB, Kjeldsen SE, et al, for the LIFE Study Group. Cardiovascular morbidity and mortality in the Losartan Intervention For Endpoint reduction in hypertension study (LIFE): a randomised trial against atenolol. *Lancet*. 2002;359:995–1003.
38. Agodoa LY, Appel L, Bakris GL, et al, for the African American Study of Kidney Disease and Hypertension (AASK) Study Group. Effect of ramipril vs amlodipine on renal outcomes in hypertensive nephrosclerosis: a randomized controlled trial. *JAMA*. 2001;285:2719–2728.